UNIVERSITI PUTRA MALAYSIA

EFFECTS OF PROBIOTIC SUPPLEMENTATION ON CALCIUM ABSORPTION AND BONE HEALTH STATUS IN OVARIECTOMIZED RATS

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By

KOLSOOM PARVANEH

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

August 2015

DEDICATION

This thesis is dedicated to my family, parents, brothers and sisters who love me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.

This work is also dedicated to my husband, Mr. Behzad Mahdian who has been a constant source of support and love. I am truly thankful for having you in my life.

Abstract of thesis presented to the senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree Doctor of Philosophy

EFFECTS OF PROBIOTIC SUPPLEMENTATION ON CALCIUM ABSORPTION AND BONE HEALTH STATUS IN OVARIECTOMIZED RATS

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Chairman: Associate professor Rosita Jamaluddin, PhD
Faculty: Medicine and Health Sciences

Osteoporosis is a bone metabolism disorder which is explained by low bone mass and deterioration of bone tissue which is mostly due to the aging or menopause. The possibility of wrist, hip or spine fracture due to osteoporosis is estimated as parallel to the risk of heart disease. Therefore, the aim of the current study is to examine the effect of probiotics (*Bifidobacterium. longum,* and *Lactobacillis. helveticus*) as a single species or double strain on calcium absorption and bone health status in ovariectomized rats.

For this purpose, 56 female Sprague–Dawley rats of 10 weeks old were used in this study. Bilateral ovariectomy (Ovx) and sham-ovx (S-ovx) were performed on the rats. After 2 weeks of surgery the rats were randomly divided into 6 groups of Ovx and one group of S-ovx. The surgical process and diet were as follow: G1: S-ovx, G2: Ovx, G3: Ovx + Ca, G4: Ovx + *B. longum,* G5: Ovx + *L. helveticus,* G6: Ovx + mixture of *L. helveticus* and *B. longum*, and G7: Ovx + mixture of *L. helveticus* and *B. longum* + Ca. The urine, fecal, and serum of the rats were collected and apparent Ca absorption and Ca retention were measured. Serum biomarkers were evaluated. Bone mineral contents (BMC) were analysed from the femur using atomic absorption spectrophotometer (AAS). BMD, trabecular structures, percentage of bone volume/total volume (BV/TV %), and percentage of total porosity were assessed using micro CT-scan. Breaking force of the femur was analysed by three point bending test using universal testing machine. Bone cellular structures were measured as static histomorphometric measurements. The fold changes of the expression of the genes were quantified with Real-time quantitative polymerase chain reaction (RT-qPCR).

The results of the research showed combination of mixed bacteria and Ca in G7 and *L. helveticus* in G5 as a single species have increased significantly BMD of the femur compared to Ovx-non treated group (0.96±0.02, and 0.90±0.05 vs 0.74±0.05 $gr.cm^{-3}$ respectively). *B. longum* treated group showed a higher Th.Th and a lower total porosity percentage ($p<0.05$) as compared to Ovx- non treated group. In addition, a higher strength of the femur have found in G7 (mixed bacteria + Ca) ($p<0.05$) (0.88±0.16 vs 0.54±0.11 $N.m^2$). Single species bacteria have increased the expression of runt related transcription factor (RUNX-2), bone morphometric protein2 (BMP-2), secreted protein acidic and rich in cysteine (SPARC), Collagen type 1 & 2 (Col 1&2), osterix (OSX), as well as calcium sensing receptor (CaSR) genes ($p<0.05$), and have decreased parathyroid receptor (PTHr) ($p<0.05$) as compared to Ovx non-treated group. However, mixed bacteria only altered the expression of CaSR, SPARC and PTHr. In addition, liver toxicity was not reported with the

selected dosage of bacteria consumption, since treated and non-treated Ovx were not significantly different in histology changes of the liver and liver serum biomarkers.

This study found that *L. helveticus*, and *B. longum* as a probiotics supplementation, have resistance to acid and bile in gastrointestinal tract. This meant that, selected bacteria after their passage through the gastrointestinal tract were alive. In this regards, single species showed a higher potential effect on changes of BMD of the femur as compared to mixed strains. Thus, *B. longum* and *L. helveticus*, specially as a single species have shown a great potential on bone health. Therefore, choosing appropriate probiotics as a single species or mixed strains is important to act on the target organ for intervention or treatment of the specific disease, such as bone in order to prevent osteoporosis.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN SUPPLEMEN PROBIOTIK TERHADAP PENYERAPAN KALSIUM DAN STATUS KESIHATAN TULANG PADA TIKUS OVARIEKTOMI

Oleh

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Pengerusi: Prof Madya Rosita Binti Jamaluddin, PhD
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Osteoporosis adalah sejenis gangguan metabolisma tulang dengan kepadatan tulang yang rendah dan kemerosotan tisu tulang kebanyakannya disebabkan oleh penuaan atau menopaus. Kemungkinan berlakunya kepatahan pada pergelangan tangan, pinggul atau tulang belakang disebabkan osteoporosis adalah dianggap selari dengan risiko penyakit jantung. Maka, tujuan kajian semasa adalah untuk mengkaji kesan probiotik (*Bifidobacterium. longum*, dan *Lactobacillis. helveticus*) sebagai spesies tunggal atau probiotik dua strain terhadap penyerapan kalsium dan status kesihatan tulang pada tikus ovariektomi.

Bagi tujuan ini, 56 ekor tikus Sprague–Dawley yang berusia 10 minggu telah zdigunakan dalam kajian ini. Ovariektomi dua hala (Ovx) dan sham-ovx (S-ovx) telah dilakukan pada tikus tersebut. Selepas 2 minggu pembedahan, tikus tersebut dibahagikan secara rawak kepada 6 kumpulan Ovx dan satu kumpulan S-ovx. Proses pembedahan dan diet adalah seperti berikut: K1: S-ovx, K2: Ovx, K3: Ovx + Ca, K4: Ovx + *B. longum*, K5: Ovx + *L. helveticus*, K6: Ovx + campuran *L. helveticus* dan *B. longum*, dan K7: Ovx + campuran *L. helveticus* dan *B. longum* + Ca. Kencing, najis dan serum tikus dikumpulkan dan penyerapan serta pengekalan Ca ketara diukur. Penanda biomarker serum telah dinilai. Kandungan mineral tulang (BMC) telah dianalisis dari tulang femur menggunakan spektrofotometer penyerapan atom (AAS). BMD, struktur trabekula, peratusan jumlah tulang/jumlah keseluruhan (BV/TV%) dan peratusan jumlah keliangan telah dinilai menggunakan imbasan tomografi terkomputasi (CT) mikro. Daya pemecahan tulang femur dianalisis pada tiga titik lenturan dengan menggunakan mesin ujian universal. Struktur sel tulang diukur sebagai ukuran histomorfometrik statik. Perubahan kuantiti replikasi ekspresi gen diukur dengan reaksi rantaian polimerasi kuantitatif masa sebenar (RT-qPCR).

Keputusan kajian menunjukkan gabungan bakteria campuran dan Ca dalam K7 dan *L. helveticus* dalam K5 sebagai spesies tunggal telah meningkat dengan ketara BMD tulang femur berbanding dengan kumpulan bukan rawatan Ovx (0.96±0.02, dan 0.90±0.05 vs 0.74±0.05 gr.cm^{-3} masing-masing). Kumpulan yang dirawat dengan *B. longum* menunjukkan Th yang lebih tinggi. Th dan jumlah peratusan keliangan dalah lebih rendah ($p<0.05$) berbanding dengan kumpulan bukan rawatan Ovx. Di samping itu, kekuatan tulang femur yang lebih tinggi telah didapati pada K7 (bakteria campuran + Ca) ($p<0.05$) (0.88±0.16 vs 0.54±0.11 N.m^{2}). Bakteria spesies tunggal telah meningkat ungkapan runt berkaitan factor transkripsi (RUNX-2), tulang morfometrik protein2 (BMP-2), protein rembesan berasid dan kaya dengan cysteine (SPARC), jenis kolagen 1 & 2 (Kol 1&2), osterix (OSX) serta gen

kalsium sensing reseptor (CaSR) ($p<0.05$) dan pengurangan resoptor paratiroid (PTHr) ($p<0.05$) berbanding dengan kumpulan bukan rawatan Ovx. Walaubagaimanapun, bakteria campuran hanya mengubah ungkapan CaSR, SPARC dan PTHr. Di samping itu, ketoksikan buah hati tidak dilaporkan dengan dos penggunaan bakteria memandangkan tiada perbezaan ketara untuk perubahan histologi pada buan hati dan biomarker serum hati antara kumpulan rawatan dan bukan rawatan Ovx.

Kajian ini mendapati bahawa *L. helveticus*, dan *B. longum* sebagai supplemen probiotik yang mempunyai daya ketahanan terhadap asid dan cecair hempedu dalam saluran gastrousus. Ini bererti bahawa bakteria terpilih masih hidup selepas melalui saluran gastrousus. Sehubungan dengan ini, spesies tunggal menunjukkan kesan potensi yang lebih tinggi ke atas perubahan BMD tulang femur berbanding dengan probiotik campuran. Oleh itu, *B. longum* dan *L. helveticus* khas sebagai spesies tunggal telahpun menunjukkan potensi yang besar terhadap kesihatan tulang. Oleh itu, pemilihan probiotik yang bersesuaian sebagai species tunggal atau jenis campuran adalah penting untuk bertindak pada organ sasaran tertentu untuk intervensi atau rawatan penyakit tertentu seperti pada bahagian tulang untuk mengelakkan osteoporosis.

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I certify that a Thesis Examination Committee has met on 10 August 2015 to conduct the final examination of Kolsoom Parvaneh on her thesis entitled "Effects of Probiotic Supplementation on Calcium Absorption and Bone Health Status in Ovariectomized Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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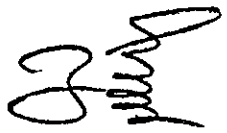

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrophotometer
AC	Attenuation coefficient
ACUC	Animal Care and Use Committee
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
Ang II	Angiotensin II
ASBMR	American Society of Bone Mineral Research
AST	Aspartate aminotransferase
ATCC	American Type Culture Collection
B. longum	*Bifidobacterium longum*
BMC	Bone mineral content
BMD	Bone mass density
BMP	Bone morphogenetic proteins
BMPRs	Bone morphogenetic proteins receptors
BMU	Basic multicellular units
bp	Base pair
BSM	Bifidus Selective Medium
BV	Bone volume
Ca	Calcium
CA	cytosine-adenin
CaHA	Calcium hydroxyapatite
CALCR	Calcitonin receptor
CaSR	Calcium-sensing receptor
CFU	Colony forming unit
Col 1 & 2	Collagen type 1 α 2
CPP	Casein phospho peptides
CTX	C-terminal telopeptid
D2	Ergocalciferol
D3	Cholecalciferol
DEXA	Dual-energy X-ray absorptiometry
ELISA	Enzyme-linked immunosorbeny assay
ER	Estrogen receptors
ERE	Estrogen response elements
ES/BS	Eroded surface/bone surface
F	Force
FGF23	Fibroblast growth factor 23
g	Gram
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GH	Growth hormone
GI	Gastrointestinal
GRAS	Generally regards as safe
H & E	Haematoxylin and eosin
HRT	Hormone replacement therapy
I	Moment inertia
IGF	Insulin-like growth factor
IGFs	Insulin-like growth factors
IL6	Interlukin 6
IP	Intra-peritoneally
IPP	Isoleucyl prolyl proline
L. helveticus	*Lactobacillus helveticus*

M	Moment
MAPK	Mitogen activating protein kinase
Mg	Magnesium
mg/L	Miligeram/Liter
mm	millimeter
mmol/L	Milimol/Liter
MRS	Man Rogosa and Sharpe
N	Nioton
NF-kB	Nuclear factor kappa B cells
ObS/BS	Osteoblast surface/bone surface
OC	Osteocalcin
OcS/BS	Osteoclast surface/bone surface
OD	Optical density
OPG	Osteoprotegerin
OS/BS	Osteoid surface/bone surface
OSF2	Osteoblast-specific factor 2
OSX	Osterix
OV/BV	Osteoid volume/bone volume
Ovx	Ovariectomized
P	phosphorus
POStn	Periostin
PTH	Parathyroid hormone
QC	Quality control
RANKL	Receptor activator of nuclear factor kappa-B ligand
RT-qPCR	Real-Time quantitative polymerase chain reaction
RUNX	Runt-related transcription factor
S	Stress
SCFA	Short chain fatty acid
SEM	Standard error from mean
SHBG	Sex hormone binding globulin
Sovx	Sham-ovariectomized
SPARC	Secreted protein acidic and rich in cysteine
TFTC	Too few to count
TGF-β	Tumor growth factor-beta
Th.N	Trabecular number
Th.Sp	Trabecular separation
Th.Th	Trabecular thickness
TMTC	Too many to count
TNF	Tumor necrosis factor
TV	Total volume
U	Unit
VDR	Vitamin D receptor
VPP	Valyl prolyl proline
Zn	Zinc

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Osteoporosis is a bone metabolism disorder, which is explained by low bone mass and deterioration of the bone tissue, which leads to increase in bone weakness, and consequently increases the possibility of fracture (Metcalfe, 2008). Seventy five million people in Europe, Japan and the United State are affected with osteoporosis. The possibility of wrist, hip or spine fracture due to the osteoporosis is estimated to be parallel to the risk of heart disease (Kai, Anderson, & Lau, 2003). Mostly osteoporosis is due to aging or the menopause in women (Ji & Yu, 2015). The life span of the women has risen worldwide (Wong & Liyana, 2007). Therefore, one third of women's life spans are spent in menopause, thus it is necessary to reduce the inverse effect of the menopause on women's health.

Sufficient calcium intake has been reported to support bone growth and reduce bone loss during the aging process. Milk and milk products supply 75% of calcium needed for the body in Western countries, but milk consumption has reduced over the past decade (Woolf & Pfleger, 2003). Some of the specialists believes that one of the effective treatments for osteoporosis specially, is the hormone replacement therapy (HRT). However, because of the side effects of HRT, this treatment is not generally accepted due to low compliance, unwillingness and aversion of many women. Moreover, long duration usage of HRT therapy leads to increase the possibility of growing some types of cancer (Picherit et al., 2000).

Some of the alternative ways for preventing and treating osteoporosis are being developed and recommended by research scientists worldwide. Exercise, including walking and light running has been reported to influence in maintaining bone mass density (BMD) (Downey & Siegel, 2006). Another possibility way for fighting osteoporosis is probiotic consumption.

The general definition of probiotics is "live micro-organisms administered in adequate amounts which confer a beneficial physiological effect on the host'' (Reid et al., 2003). During the last decade of the 20th century, when the term of functional foods were defined clearly, probiotics became popular. Nowadays, the public aware of probiotics as dietary supplements and the components of bio-yoghurts (Woolf & Pfleger, 2003).

1.2 Problem Statement

Osteoporosis is the most prominent bone disease and it is considered as a serious public health concern, because of its prevalence worldwide. Generally, in The United States and in the Europe, 30% of all postmenopausal women suffer osteoporosis. It is estimated that, approximately one out of five American women over the age of 50 suffer from this disease. Almost 50% of all women and 15-30% of men over 50 years of age, face risk of fractures of the hip, wrist, or vertebra due to the osteoporosis. The ageing populations as well as postmenopausal condition in women are considered as a major contributor to the osteoporosis (Woolf & Pfleger, 2003).

One of the most common issues faced by osteoporosis patient is hip fracture (Kanis et al., 2007). Risk of hip fracture among women due to menopausal and osteoporosis, are more rather than men. Risk of fracture for 50 years old women was reported at 53.2% versus 20.7% risk of fracture for men for the same age (Staa, Dennison, Leufkens, & Cooper, 2001). The rate of hip fractures is rising throughout the world, and the researchers estimate this rate by 2050 to be 6.3 million worldwide. The rise will affect in particular, Asian countries. In addition, more than 50% of all hip fractures worldwide are estimated to be from Asia by 2050 (Dhanwal, Dennison, Harvey, & Cooper, 2011). The Asian population has shorter height and less body mass index (Babbar et al., 2006). It is shown that lower height and body mass index can increase the likelihood of osteoporosis disease (Munaisinghe, Botea, & Edelson, 2002). In addition, geographical variations in Asia have moderate effect in the incidence of hip fracture. In comparison of four countries in Asia, such as Singapore, Hong Kong, Thailand and Malaysia, the rates of hip fracture in Singapore and Hong Kong were similar. However, in Thailand were 60% and in Malaysia were 50% of the rates in Hong Kong (Lau et al., 2001).

One of the ways of treatment for menopausal osteoporosis is HRT, but this treatment have shown the side effects such as breast cancer (Hou et al., 2013; Marsden, 2002; Picherit et al., 2000). Therefore, an alternative way of reducing or fighting osteoporosis is needed. In this regard, probiotic is now growing in importance (Scholz-Ahrens et al., 2007). Some previous studies have shown specific changes of gut microbiota through the use of probiotics and have a possible effect on the improvement of bone health in ovariectomized (Ovx) rats which stimulate postmenopausal conditions (Jirillo et al., 2012; McCabe, Irwin, Schaefer, & Britton, 2013; Scholz-Ahrens et al., 2007). Additionally, Chiang and Pan, (2011) have shown the effect of *Lactobacillus plantarum* and *Lactobacillus paracasei* with the dosage of 10^8 CFU/ml on trabecular bone. Besides, Scholz-Ahrens et al., (2007) carried out on *Lactobacillus casei*, *Lactobacillus reuteri,* and *Lactobacillus gasseri* and reported these strain of probiotics stimulate higher apparent calcium absorption among the rats, as well as 35% higher bone weight.

Although some treatments have shown to reduce osteoporosis among menopausal women, but still osteoporosis and fracture risk is one of the main problems among post-menopausal women. This indicates a high demand for introducing prophylactic measures to reduce the inverse health effects of the menopause such as osteoporosis among women or reducing osteoporosis prevalence. Therefore, the present study aimed to determine the effect of two different probiotic strain (*L. helveticus and B. longum*) as a single or mixed strain on Ca absorption and bone health status in Ovx rats.

1.3 Significance of the Study

Although a few earlier studied reported on the effect of probiotics on bone health (Rodrigues et al., 2012; Chiang & Pan, 2011; Kim et al., 2009), but little known about the effectiveness of probiotic as a single strain compared to mixed strain. This study is the first, which assessed the potential effect of double strains of probiotic (*Bifidobacterium longum* and *Lactobacillus helveticus*), and compared with the effect of single strain on Ca bioavailability and bone health status. This study also is the first to evaluate the effectiveness of Ca supplementation on the action of *B. longum* and *L. helveticus*.

Besides, the knowledge about the genetic factors of osteoporosis are important, because, they may propose the use of genetic markers for the evaluation of the risk of osteoporosis and this gives an opportunity to recognize new targets for new drugs or supplements, or fortification of food for the prevention or treatment of osteoporosis. Due to this, the expression of some estrogenic gens was evaluated in this study. In addition, variables related to liver function were assessed and the toxicity of consumption of the selected dosage of bacteria on liver system reported. Determinant of toxicity of the proposed drug or supplement is important, that it is to be accepted as a diet supplement.

In fact, this research can bring a new knowledge on the potential effect of probiotics bacteria as a single species, and compare it with double strains on Ca absorption and bone health status as well as its safety with the selected dosage as a dietary supplement.

1.4 Objectives

1.4.1 General Objective

To investigate the effect of double strain probiotics supplementation (*L. helveticus* and *B. longum*) and compared with single strain on calcium absorption and bone health status in Ovx-induced bone loss rats.

1.4.2 Specific Objectives

I. To determine the effect of *L. helveticus* and *B. longum* as a single species or double strain and Ca supplementation on BMD, BMC and bone cellular structure changes of Ovx- induced bone loss rats.
II. To determine the effect of *L. helveticus* and *B. longum* as a single species or double strain and Ca supplementation on the strength of the bone of Ovx-induced bone loss rats.
III. To measure Ca excretion from urine and feces of the rats and evaluate apparent calcium absorption and calcium retention among control and intervention groups.
IV. To determine the effect of *L. helveticus* and *B. longum* supplementation as a single species or double strain on serum indicator of bone formation and resorption.
V. To investigate the effect of probiotics supplementation (*B. longum* and *L. heveticus*) as a single species or double strain on bone histology in Ovx-induced-bone loss rats.
VI. To determine and compare the quantity expression of some genes affected by *B. longum* and *L. heveticus* as a single species or in combination in Ovx-induced-bone loss rats.
VII. To determine the liver toxicity of selected dosage of probiotics supplementation (*B. longum* and *L. heveticus*) in Ovx induced-bone loss rats and compare with control groups.

1.5 Research Question

a) Does probiotics supplementation (*L. helveticus* or *B. longum*) increase Ca absorption and bone mass density in Ovx induced-bone loss rats?
b) Does supplementation with double strain probiotic (*L. helveticus* and *B. longum*) increase Ca absorption and bone mass density more than single strain?

1.6 Research Hypothesis

a) This study hypothesized that, *L. helveticus* or *B. longum* increase Ca absorption and bone mass density in Ovx rats and double strain of probiotic supplementation (*L. helveticus* and *B. longum*) boost calcium absorption and bone mass density more as compared to single strain
b) Supplementation of probiotics with Ca has more effect on Ca absorption and bone mass density as compared to probiotic alone.

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